Natural killer cells- from innate cells to the discovery of adaptability

Débora Basílio-Queirós* and Eva Mischak-Weissinger

Hannover Medical School, Department of Hematology, Hemostasis, Oncology and Stem Cell Transplantation, Hannover, Germany

Natural Killer (NK) cells have come a long way since their first description in the 1970's. The most recent reports of their adaptive-like behavior changed the way the immune system dichotomy is described. Adaptive NK cells present characteristics of both the innate and adaptive immune system. This NK cell subpopulation undergoes a clonal-like expansion in response to an antigen and secondary encounters with the same antigen result in an increased cytotoxic response. These characteristics can be of extreme importance in the clinical setting, especially as adoptive immunotherapies, since NK cells present several advantages compared other cell types. This review will focus on the discovery and the path to the current knowledge of the adaptive NK cell population.

Background

The immune system is classically divided in two branches, the innate and adaptive immunity according to the cellular characteristics. The innate branch of the immune system offers a fast but unspecific response against pathogens. The adaptive immune system recognizes antigens/pathogens and cells are clonally expanded and, in the case of antigen-specific B-cells, even modified to obtain higher levels of antigen specificity (1–5).

Innate lymphoid cells (ILCs) comprise a variety of common lymphoid progenitor-derived cells that do not express somatically rearranged antigen-specific receptors and play important roles in immune homeostasis. One subset of ILCs are Natural Killer (NK) cells (6–8). In humans, they comprise between 5 to 20% of circulating lymphocytes (9). These immune cells have very diversified functions that can range from their classic innate anti-tumor and anti-viral functions, to regulatory roles involved in the modulation of other immune cells as well as tissue growth promotion (10).

NK cells were first described in the early 1970's when a significant natural cytotoxicity to target cells was observed in lymphocytes from unimmunized mice and normal human lymphoid tissue (10–13). Until then, it was believed that non-T cell-mediated cytotoxicity was only achieved by antibody-dependent-cell-cytotoxicity (ADCC) or macrophages (14–16). R. Kiessling et al. were able to exclude a possible involvement of macrophages, T and B

cells. This was achieved by the combined results observed in athymic nude mice and inability to identify the aforementioned cells. A new and unique cell population able to kill mouse tumor cells was hence recognized. Even though very little was known about this cell population, this observation opened the door to a brand-new world in immunology (11). We have come a long way in our knowledge about NK cells since these days.

In the following sections, this review aims to summarize the evolution in NK cells knowledge from their discovery to the detection of their adaptive phenotype.

Natural killer cells biology and receptors

Natural Killer cells were the first member of the ILC family to be discovered. They possess a lymphoid developmental origin and a T-bet-regulated rapid cytokine production activation profile. However, this activation does not lead, generally, to immunological memory. Furthermore, NK cells lack clonally rearranging antigen receptors (17). This was demonstrated in mice, where RAG-1 or RAG-2 disrupted genes did not affect the development of functional NK cells (18, 19). It is known that NK cells are involved in the immune response to several pathogens and are also involved in the first line of defense against tumor cells without prior sensitization (20–23). NK cells were normally characterized according to their morphology, as large granular lymphocytes and phenotypically, defined by the surface expression of the cluster of differentiation (CD)56 and lack of CD3 (24). Another definition of mature conventional NK cells relies on exclusion criteria describing NK cells as non-T, non-B lymphoid cells with the ability to rapidly produce interferon (IFN)-gamma upon stimulation with pathogens (25).

NK cells are bone marrow derived and can be found in the peripheral circulation, but are also present in other lymphoid and non-lymphoid organs (26). Two major distinct populations of circulating NK cells are recognized according to the surface expression of CD56 and CD16. It is considered that $CD56^{dim}CD16^{+}$, corresponding to approximately 90% of peripheral blood NK cells, represent a more cytotoxic population while the $CD56^{bright}CD16^{dim/-}$, corresponding to the remaining 10%, have a more regulatory role, being highly involved in the production of cytokines (27–29). There is, however, a much higher count of NK cells subpopulations when it comes to the different receptors expressed by these cells. For instance, in 2009, Milush et al. reported new subpopulations of NK cells based on the expression of CD7, a marker shared with T and pre-B cells. The surface expression of this receptor was associated with the co-expression of other NK cell-associated receptors such as Killer-Immunoglobulin Receptors (KIRs) or Natural Cytotoxicity receptors (NCRs) (30). With the help of technological advancement, and the possibility to simultaneously analyze more than 30 parameters, Horowitz et al. indicated that at least 30 000 different phenotypes of conventional peripheral blood NK cells can be present at any given point (31). The great diversity of NK cells populations among each individual or patient, comprising different functions and degrees of maturation, may result in varied responses. The challenge to current

research is to understand how these different populations can be exploited in the design of specific therapies.

Different NK cell subpopulations can have different, more or less specialized, functions and responses. Nonetheless, a very strict balance between activating and inhibitory receptors regulates all NK cells. Contrary to what happens with adaptive cells, NK cell receptors are germline-encoded with no requirements for recombination and the activation status of NK cells is determined by the balance between activating or inhibitory signals. A key regulator of NK cell activation is the constitutively expressed Major Histocompatibility Complex (MHC) class I. MHC class I molecules bind to the inhibitory receptors, including members of the Killer Immunoglobulin-like Receptor (KIR) family and prevent NK cell activation (32). However, infected, tumor-transformed or stressed cells, undergo a downregulation or even loss of MHC class I expression. This will result in a lack of inhibitory, or rather a prevalence of activating signals, tipping the balance towards the activation of NK cells (33, 34). This mechanism allows for the preservation of 'self' while engaging in the elimination of the 'missing-self' (32).

The activating receptors of NK cells include receptors belonging to the C-type lectins family and NCRs mentioned above. NCRs (e.g. NKp30, NKp44, NKp46 and NKp80) arm NK cells with the ability to effectively kill tumor-transformed cells (35–38). The key role of NCRs in the elimination of tumor cells is well established and can be demonstrated, for instance, by an ineffective clearance of certain tumors in the absence of NKp46 in *in vitro* and *in vivo* models (39–41). Furthermore, NCRs are also implicated in the control and clearance of pathogens. For instance, NKp46 is essential to the elimination of virus and bacteria *in vivo*. This was demonstrated by the inability of NKp46-deficient mice to recognize and eliminate influenza-infected cells expressing NKp46-ligands or as observed by the reduced activation and IFN-gamma production during the early stages of *Streptococcus pneumoniae* infections (42, 43). In regards to C-type lectins, CD94 forms covalent bonds with members of the NKG2 family (A, C, D and E) and forms heterodimers expressed by NK cells and a subset of cytotoxic T lymphocytes (44).

An overview of some inhibitory and activating receptors expressed at the surface of NK cells is summarized in Table 1.

Besides their ability to recognize and kill tumor and virus-infected cells, NK cells are also able to interact with other cell types and orchestrate the adaptive immune response. Most notably, NK cells are able to modulate Dendritic cells (DCs), macrophages and T cell (57–59). One particular example of this modulatory capability is seen, for instance, by the ability of NK cells to edit the maturation of autologous DCs through NKp30-mediated elimination of aberrant or immature DCs while sparing fully matured DCs. This results in a correct DC-priming and subsequent antigen-specific T cell response (60, 61).

Natural killer cells; innate or adaptive?

By definition, memory or adaptive cells are a population of long-lived, self-renewing immune cells with the ability of antigen-

TABLE 1 Human NK cell Activating and Inhibitory Receptor Families.

Family	Members	Molecular Structure	Function
KIR	KIR2DL1 (45)	Immunoglobulin Superfamily	Inhibitory
	KIR2DL2 (46)		Inhibitory
	KIR3DL1 (47)		Inhibitory
	KIR3DL3 (48)		Inhibitory
	KIR2DS1 (49)		Stimulatory
	KIR2DS2 (50)		Stimulatory
	KIR2DS4 (51)		Stimulatory
NCR	NKp30 (35)	Immunoglobulin Superfamily	Stimulatory
	NKp46 (37)		Stimulatory
	NKp80 (52)		Co-stimulatory
	NKp44 (38)		Stimulatory
NKG2 family	CD94/NKG2A (53)	C-type Lectins	Inhibitory
	CD94/NKG2C (54)		Stimulatory
	CD94/NKG2D (55)		Stimulatory
	CD94/NKG2E (56)		Stimulatory

specific recognition and memory formation. For many years, conventional NK cells were described as short-lived innate lymphocytes lacking antigen specificity. However, in recent years this idea has been challenged. Murine studies showed the ability of NK cells to acquire selective memory. This phenomenon was demonstrated by hapten-induced contact hypersensitivity and recall responses in challenged mice, lacking mature T and B cells. This feature was previously widely accepted as a T cell effect. Furthermore, this NK cell response persisted for several weeks and was able to discriminate between different haptens. This assembles three hallmarks characteristics of adaptive immunity: i) acquired activity, ii) antigen specificity and iii) long-lived memory cells (62). The hapten-specific response was further characterized by Paust et al., while the NK cell memory development in response to different viruses and possible influence of the host's genetic background was also assessed. To elucidate this memory function, non-infectious virus-like particles containing proteins from influenza or HIV and UV-inactivated vesicular stomatitis virus were used. Immunization of naïve Rag1$^{-/-}$ mice and subsequent adoptive transfer of purified NK cells into naïve Rag2$^{-/-}$Il2rg$^{-/-}$ mice resulted in a vigorous and sustained response at challenge 4 weeks later. This response was virus-specific and restricted to hepatic NK cells isolated from immunized mice, while splenic NK cells were unresponsive. Furthermore, this NK cell-specificity persisted for at least 4 months (63). Another study described the ability of NK cells to develop a memory-like behavior following cytokine stimulation. The *in vitro* stimulation consisted of a combination of interleukin (IL)-12, IL-15 and IL-18. NK cells were then adoptively transferred to naïve Rag1$^{-/-}$ mice and re-stimulation with IL-12 and IL-15 or *via* the engagement of activating NK cell receptors with antibodies led to a robust IFN-gamma secretion. Furthermore, the often termed 'memory-like' NK cells in this experimental setting, produced significantly higher levels of IFN-gamma which was detected for at least 3 weeks post-adoptive transfer of pre-activated NK cells (64).

The particular role of Cytomegalovirus

Gumá et al. described the expansion of a population of NK cells in response to cytomegalovirus (CMV)-infected fibroblasts in 2006 and this set off increasing interest in NK cell function thus accumulating knowledge over the last decade (21). The NK relationship with CMV has for long been appreciated by the observation of the high susceptibility to CMV-infections in both humans and mice lacking functional NK cells (65–69).

Murine models facilitated the intensive study of the NK cell-CMV molecular mechanisms. This was largely simplified by the identification of both receptor and ligand involved in the NK cell memory formation. The murine NK cell activating receptor Ly49H recognizes the m157 protein expressed on infected cells (70). Multiple factors have been identified as essential for the NK cell memory development during murine CMV (MCMV) infection at different stages. These include IL-12/STAT4 signaling, IL-18, miR-155, the Bim protein, the Zbtb32 transcription factor, recombination-activation genes and mitophagy (71–76). In MCMV, contrary to Paust et al. hapten-induced contact hypersensitivity study, adaptive NK cells were found in the liver but also in the spleen, lung, kidney, blood circulation and other lymphoid tissues. This population of NK cells underwent an expansion phase, followed by a contraction phase after resolution of viral infection and ultimately resulted in the generation of long-

lived "memory" NK cells that were more protective during a second encounter with this pathogen (77, 78).

In humans, it is now known that this particular NK cell behavior is associated to the non-classical MHC class I molecule HLA-E and its antigenic presentation of human CMV (HCMV) viral peptide(s) to NKG2C, which is a C-type lectin that covalently bonds to CD94 (79). In HCMV, conflicting information regarding the expansion of this cell population was reported. Several studies described the expansion of NKG2C+ NK cells in other viral infections. These ranged from HIV, Hantavirus, Chikungunya virus, Hepatitis B virus and Epstein-Barr virus (80–86). Interestingly however, the expansion of NKG2C+ NK cells was almost completely limited to the HCMV seropositive population in all the studies in which CMV status was assessed. This suggests that HCMV is the common denominator in the expansion of NKG2C+ NK cells (80, 81, 85, 86). This supported the previous observation of Gumá et al. that HCMV influences the shaping of the NK cell receptor repertoire. Furthermore, the expansion of NKG2C+ NK cells was not seen in the context of other herpesviruses infections. Thus, HCMV may be unique in its ability to recall NKG2C+ NK cells responses (66, 87).

The diversity within NK cells may be the result of what has been described as an 'arms race' between NK cells and viruses (88) [74]. CMV infection results in the modulation and downregulation of MHC class I molecules on the surface of infected cells in an attempt to escape recognition by T cells (89). In fact, in the case of infected-cells being eliminated by class I-restricted CD8+ cytotoxic T lymphocytes (CTLs), pathogens that attenuate class I expression will become invisible, at least temporarily, to CTLs and therefore, have a selective advantage. In CMV-infection, this is achieved by different approaches. For example, the transport of peptides produced in the cytosol can be affected by the HCMV US6 gene attacking the TAP complex and preventing class I heterodimers from binding (90). Other strategies may be related to the retention or destruction of class I molecules. The US3 gene product binds to class I molecules sequestering them in the endoplasmic reticulum (91). Furthermore, US2 and US11 products bind to class I molecules and redirect the class I heavy chain to the cytosol, reversing the process by which the chain is inserted in the endoplasmic reticulum (92). This CTL evasion mechanism can, however, lead to the engagement of a NK cell response. NK cells are usually prevented from activation by the engagement of inhibitory receptors by self-MHC products. Certain viruses are capable of successfully reducing the surface expression of MHC class I, while controlling NK cell activation by the expression of class I homologues that will serve as decoys for NK cells. In the case of CMV, examples of this are UL18 in humans and m144 in mouse. In the particular case of UL18, this viral homologue binds to inhibitory receptors with higher affinity than MHC class I (93–95). Furthermore, the HCMV UL40 open reading frame, contains a segment that is homologous to the HLA-E binding leader peptide (96). However, the efforts of CMV to circumvent the immune system go one step even further. HCMV harbors a unique IL-10 homolog (cmvIL-10) which is able to compete with human IL-10 for binding sites (97). This viral cmvIL10 may facilitate HCMV replication by suppressing or tampering with inflammatory responses. Furthermore, a study by Chang et al. showed that the production of cmvIL-10 inhibits the production of IL-12 and tumor necrosis factor (TNF)-alpha by DCs in a concentration-dependent manner (98). As IL-12 promotes the cytotoxic and proliferative capacity of NK cells, cmvIL-10 may inhibit or delay the activation NK cells both directly and indirectly. All these mechanisms employed by CMV to evade NK cell-recognition point to the importance of NK cells in the control of CMV.

Interestingly however, cmvIL-10 was shown to induce NK cell activation and the increased NK cell cytotoxicity was triggered by several activating receptors. cmvIL-10 binds to the IL-10 receptor (IL-10R). Even though IL10-R is expressed at low levels on NK cells, the production of a virokine able to activate NK cells by HCMV is puzzling (99). One may hypothesize that the low level of activation promotes a pro-inflammatory environment beneficial for HCMV infection and/or dissemination all the while ensuring that a strong enough trigger does not result in an effective antiviral response.

Epigenetic profile towards adaptivity

The NK cell population is one of great heterogeneity both in phenotype and function. CMV was shown to directly influence the NK cell population and lead to lasting alterations (87, 100). Furthermore, CMV was also shown to influence the outcome after hematopoietic stem cell transplantation of acute and chronic myeloid leukemia patients since CMV reactivation controlled by CMV-CTLs led to decreased relapses in these patients (101, 102). A recent study by our group demonstrated that adaptive NK cells have the ability to recruit T cells when cultured with CMV-infected target cells (103). However, at the molecular level, the receptor modulation and NK cell differentiation has not yet been described. A study by Schlums et al. shed some light on these questions. The analysis of 196 healthy adults showed that the CD56dim NK cell population from many donors lacked expression of the adaptor protein FcεRγ, the tyrosine kinase SYK and the intracellular adaptor protein EAT-2 (50.4% of HCMV seropositive donors vs 10.1% of HCVM seronegative donors). They demonstrated that this effect correlated to HCVM seropositivity regardless of sex and age of the donor, B cell or myeloid-cell-related signaling proteins. Furthermore, this was observed only in acute HCMV infection (de novo or reactivation). The lack of FcεRγ, SYK and EAT-2 correlated with phenotypic characteristics of adaptive NK cells, namely, the expression of NKG2C and absence or reduced expression of NKp30. Deficiency for EAT-2 and FcεRγ was shown to be the result of hypermethylation in their promoter region (104). Similar results were observed for SYK by Lee et al. (105). Moreover, genome-wide analysis of DNA methylation comparing canonical and adaptive NK cells to T cells were performed. This revealed that the methylation profile of adaptive NK cells was closely related to the one of effector T cells. Adaptive NK cells had 2372 differentially methylated regions (DMRs) compared to canonical NK cells while

only differing in 61 DMRs when compared to CD8$^+$ T cells. Furthermore, this methylation profile was responsible for the regulation of the gene expression on adaptive NK cells (104).

Origins of natural killer cell memory

Nagler et al. originally described CD3$^-$CD56^{dim} and CD3$^-$CD56^{bright} as subpopulations of NK cells in different differentiation stages, where the CD3$^-$CD56^{bright} mature overtime to the CD3$^-$CD56^{dim} population (28). The GATA-binding factor 2 (GATA-2) transcription factor is necessary for hematopoietic stem and progenitor cell survival and proliferation. Its haploinsufficiency results in deficiencies in Dendritic, B and NK cells and leads to clinical symptoms of immunodeficiency, lymphedema and even myelodysplastic syndrome (106, 107). A more recent analysis and characterization of symptomatic GATA-2 (+/- or mutation) patients' showed that persisting NK cells displayed characteristics and functional properties of adaptive NK cells. Taken this into account, adaptive NK cells would be able to persist in the absence of their CD56^{dim} precursors raising questions onto the ontogeny of adaptive NK cells. Characteristics of persisting NK cells included a decreased expression of the promyelocytic leukemia zinc finger (PLZF) and T-box transcription factors (T-bet), maintained Fc receptor expression and cytotoxic capacity in response to antibody-coated target cells, as well as, degranulation capacity and IFN-gamma and TNF secretion. Furthermore, the persistence of this cell population despite the GATA-2 insufficiency that results in the abolishment of canonical NK cells demonstrates the considerable increased longevity of adaptive NK cells (108). Another study provides further evidence into the longevity of adaptive NK cells and further supports a self-renewal hypothesis. Here, paroxysmal nocturnal hemoglobinuria patients have an X-linked acquired Phosphatidylinositol N-acetylglucosaminyltransferase subunit A (PIGA) mutation. PIGA encodes a protein required for the synthesis of glycosylphophatidylinositol (GPI) anchors. These loss-of-function mutations occur in hematopoietic stem and progenitor cells, and result in the production of hematopoietic cells deficient in GPI-anchored membrane proteins (109). Progression of the disease from a GPI^{pos}/GPI^{neg} mixed chimerism towards a virtually exclusive GPI^{neg} lineage can give insight into the development of adaptive NK cells. Results from 15 patients suggested that CD56^{dim} NK cells may persist and propagate independently of CD56^{bright}. Furthermore, the majority of adaptive NK cells where GPI^{pos}, while canonical NK cells were vastly GPI^{neg}. Consistent with prior studies, GPI^{pos} adaptive NK cells showed marked reduction in IFN-gamma production in response to co-stimulation with IL-12 and IL-18 innate cytokines while maintaining degranulation capacity upon engagement of the low affinity Fc receptor CD16. This indicates that the described long-lived GPI^{pos} NK cells are functionally comparable to adaptive NK cells (110). These studies suggest a peripheral pathway for the maintenance of CD56^{dim} adaptive NK cells independent of hematopoietic stem and progenitor cells production and also independent of CD56^{bright} precursor (108, 109). A linear model representation of the developmental pathway of (adaptive) NK cells is shown in Figure 1.

Importance in health and disease

Natural Killer cells play a role in the most varied biological processes and are involved in both health and disease. These range
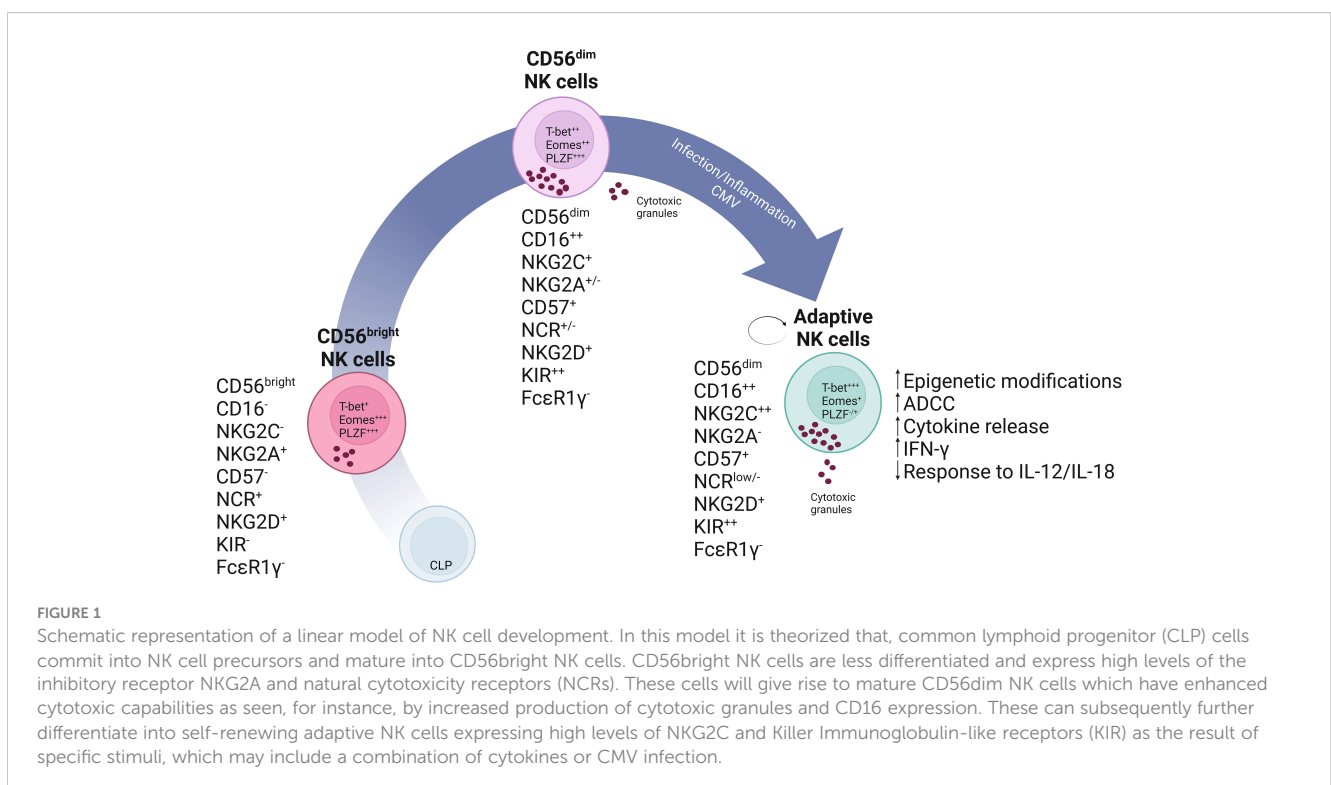

FIGURE 1

Schematic representation of a linear model of NK cell development. In this model it is theorized that, common lymphoid progenitor (CLP) cells commit into NK cell precursors and mature into CD56bright NK cells. CD56bright NK cells are less differentiated and express high levels of the inhibitory receptor NKG2A and natural cytotoxicity receptors (NCRs). These cells will give rise to mature CD56dim NK cells which have enhanced cytotoxic capabilities as seen, for instance, by increased production of cytotoxic granules and CD16 expression. These can subsequently further differentiate into self-renewing adaptive NK cells expressing high levels of NKG2C and Killer Immunoglobulin-like receptors (KIR) as the result of specific stimuli, which may include a combination of cytokines or CMV infection.

from combating infections, cancer, autoimmune disorders and even in the maintenance of normal pregnancy. NK cells contribute to the control of viral infections by both, direct cytotoxicity against virally-infected cells, but also by the production of cytokines that may control viral replication and regulate an adaptive immune response [103]. They are also involved in the elimination of other types of infection that include infections caused by intracellular bacteria, fungi and some protozoa [111]. One other important function of Natural Killer cells is the elimination of tumor cells. In this scenario, NK cells' most likely role is the surveillance and elimination of malignant cells in order to prevent the formation of tumors. In regards to autoimmune disorders such as lupus erythematosus, NK cells can play a role in tolerance induction, by decreased numbers and activity, increased proportion of CD56^{bright} cells and impaired cytotoxicity [112–114]. NKp46, a NCR NK cell's receptor, has been involved in the pathophysiology of type 1 diabetes while in rheumatoid arthritis, a subset of Natural Killer cells is greatly expanded in patients with inflamed joints [115, 116]. NK cells also play an essential role in the efficacy of some vaccines and immunotherapies, such as seen as the result of, for instance, the BCG vaccine [117]. NK cells further cooperate in vaccine efficacy through their interaction with vaccine-induced antibodies with NK cell-activation properties on top of the virus-neutralizing properties [118]. All this demonstrates the immense possibilities of NK cells in clinical applications.

Conclusion

If NK cells are believed to be an evolutionary bridge between innate and adaptive immunity, it is not surprising that they will exhibit features of both. Implications of NK cells in such mixed processes and the recent discovery of their adaptive profile demonstrates that the exploitation of this cell population and their use in possible therapeutic approaches can have great implications in health and disease. For these reasons, further research in the full range of possible applications of adaptive NK cells is warranted.

Author contributions

DB-Q contributed to the concept and design of the article. EM-W revised the article critically for important intellectual content. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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